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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte STEPHEN GILL and STANLEY FRANCIS RUSHOWSKI

Appeal 2009-003638[1]
Application 10/069,691
Technology Center 1600

Decided: August 27, 2009

Before LORA M. GREEN, FRANCISCO C. PRATS, and
MELANIE L. McCOLLUM, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to compositions containing radiopharmaceutical metal complexes in containers which have silica coatings on their inner surfaces. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

[1] GE Healthcare Limited is the real party in interest (App. Br. 1).

STATEMENT OF THE CASE

Claims 1-14 are pending and on appeal (App. Br. 1).[2] Claims 1, 6, 10 and 11, the independent claims, are representative and read as follows:

> 1. In a composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface, the improvement being that the radiopharmaceutical comprises a coordination complex of a metal with an organic ligand.
>
> 6. A kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica coating on the inner surface.
>
> 10. A composition for the preparation of a stabilized radiopharmaceutical metal complex which comprises (i) a stabilizer capable of stabilizing said radiopharmaceutical metal complex; and (ii) an organic ligand which forms a coordination complex with the metal; in a container which has a silica coating on the inner surface.
>
> 11. A composition for the preparation of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface.

The Examiner cites the following documents as evidence of unpatentability:

Crane et al.	US 5,961,952	Oct. 5, 1999
Walther et al.	US 6,200,658 B1	Mar. 13, 2001
Schott Glaswerke (as translated)	DE 29,609,958 U	Oct. 2, 1996
Yamaguchi et al.	JP 11-99192	Apr. 13, 1999

[2] Appeal Brief filed May 9, 2008.

(as translated)

The Examiner has rejected claims 1-14 under 35 U.S.C. § 103(a) as being unpatentable over Crane and Yamaguchi in view of Schott Glaswerke or Walther (Ans. 4-8).[3]

OBVIOUSNESS

ISSUE

The Examiner cites Crane as disclosing "a radiopharmaceutical comprising a complex with an organic ligand and metal and a kit which may comprise one or more vials and a bacteriostat" (Ans. 4-5). The Examiner concedes that Crane "fails to disclose that the container (e.g., vial) [has a] silica coating on the inner surface" (*id.* at 5).

To meet that limitation, the Examiner cites Yamaguchi as disclosing "containers for pharmaceutics which can prevent highly adsorbable radiopharmaceuticals from being adsorbed thereon," the containers having "an interior surface that is coated with silica" (*id.*). The Examiner also cites Walther as disclosing the use of silica coatings on the inner surfaces of hollow glass bodies "to avoid a disadvantageous dealkalizing process" (*id.* at 6). The Examiner further cites Schott Glaswerke as disclosing a glass container for storing pharmaceutical or diagnostic solutions in which the "problem of leaching of ions out of the glass was solved by coating the interior surface of the glass container with a layer of an SiO2" (*id.*).

Based on these teachings, the Examiner finds that a "skilled artisan would have been motivated to use a silica coated glass interior in the invention of Crane et al in order to take advantage of one or all [of] the

[3] Examiner's Answer mailed July 24, 2008.

advantages known in the art to be associated with silica coated interiors" (*id.* at 7).

Appellants contend that the Examiner failed to make a prima facie case of obviousness because the cited references do not teach or suggest all of the limitations in the rejected claims, and because the references do not provide motivation for combining them with each other (App. Br. 4). Specifically, Appellants assert that Crane contains only a passing reference to the vials containing its radiopharmaceutical metal complexes, and the remaining references do not disclose that their silica-coated containers can be used with radiopharmaceutical metal complexes (*id.* at 5; *see also* Reply Br. 5 (urging that Schott Glaswerke's disclosure does not relate to radiopharmaceuticals)).

Moreover, Appellants argue, Yamaguchi solves the problem of adsorption of ionic radiopharmaceuticals to the containers' inner surfaces, as opposed to complexed metals, and therefore would not have prompted an ordinary artisan to modify the inner surface of Crane's metal complex-containing vials (App. Br. 6; *see also* Reply Br. 6). Also, Appellants argue, given the many coatings capable of being used, the many features in Crane capable of variation or improvement, and the fact that Crane gives little consideration to the properties of its vials much less their inner surfaces, the Examiner's conclusion that it would be obvious to apply the specifically claimed coating to the inner surface of Crane's vials amounts to impermissible hindsight (App. Br. 7-9; *see also* Reply Br. 3-4 (pointing out that Walther and Schott Glaswerke disclose a number of coatings in addition to silica)).

Appellants further argue that, given Crane's disclosure of the use of a solubilization aid for its radiopharmaceutical metal complexes, an ordinary artisan would not have been prompted by Yamaguchi to put a silica coating on the inner surface of Crane's containers, "in that the absence of the 'solubilization aid' would remove an essential teaching of Crane. Accordingly, combining Crane and [Yamaguchi] in this manner is an invalid combination" (App. Br. 10; *see also* Reply Br. 9).

Appellants further argue that the references teach away from the claimed combination of features because an ordinary artisan, "even if assumed to be contemplating improvements of Crane, would focus on the specific teachings in Crane of embodiments taught to be important, and be motivated to improve those elements" rather than the barely mentioned vial (App. Br. 11). Moreover, Appellants urge, the "present invention is a selection invention where unexpected advantages for radiopharmaceuticals that are metal complexes of ligands have been found. The novelty lies in the selection, where the claimed subject matter has unforeseen advantages" (Reply Br. 7; *see also id.* at 8-9).

In view of the positions advanced by Appellants and the Examiner, the issue with respect to this rejection is whether Appellants have shown that the Examiner erred in concluding that an ordinary artisan would have considered it obvious to provide the inner surfaces of Crane's radiopharmaceutical metal complex-containing vials with a silica coating as taught in Yamaguchi, Walther, and Schott Glaswerke.

FINDINGS OF FACT ("FF")

1. Crane discloses a "method of using ^{99m}Tc-tertiary-butyl isonitrile complex and its analogs as breast tumor diagnosing or imaging agents and a kit for diagnosing or imaging breast tumors" (Crane, col. 1, ll. 8-11).

2. Crane discloses that the radionuclide complex-containing composition used to diagnose and image the tumors is "formed from a sterile, non-pyrogenic, kit, comprising:

(a) a predetermined quantity of tertiary-butyl isonitrile;

(b) a solubilization aid; and,

(c) a predetermined quantity of a reducing agent."

(*Id.* at col. 2, ll. 32-36.)

3. Crane discloses:

> Kits in accord with the present invention . . . optionally [contain] other components such as transfer ligands, buffers, lyophilization aids, stabilization aids, and bacteriostats. The inclusion of one or more optional components in the formulation will frequently improve the ease of synthesis of the radiopharmaceutical by the practicing end user, the ease of manufacturing the kit, the shelf-life of the kit, or the stability and shelf-life of the radiopharmaceutical. The improvement achieved by the inclusion of an optional component in the formulation must be weighed against the added complexity of the formulation and added cost to manufacture the kit. Preferably, kits according to the present invention contain a solubilization aid due to the inherent difficulties of manipulating TBI [(tertiary-butyl isonitrile)].

(*Id.* at col. 5, ll. 22-37.)

4. Crane discloses:

> The present kits may be contained in one or more vials and all or part of the formulation can independently be in the form of a sterile solution or a lyophilized solid. It is preferred

> that TBI [(tertiary-butyl isonitrile)] and reducing agent be lyophilized, when possible, to facilitate storage stability. Preferably a solubilization aid is present to ease removal of TBI upon reconstitution. If lyophilization is not practical, the kits can be stored frozen or in solution at room temperature. The solvents used are usually water or saline, preferably, water. Preferably, the kits are sealed.

(*Id.* at col. 5, ll. 38-47.)

5. A solution of the radioactive ^{99m}Tc-TBI complex suitable for imaging breast tumors can be prepared from a vial containing the ingredients of the kit as follows:

> The vial can be reconstituted by aseptic introduction through the rubber stopper seal using a syringe of a ^{99m}Tc solution, preferably ^{99m}Tc-pertechnetate in saline, in the amount of 1 mCi to 1000 mCi, preferably from 10 mCi to 100 mCi, in a volume of 0.1 mL to 10 mL, preferably 1 mL to 5 mL. The vial is then allowed to react at room temperature or it is heated at temperatures up to 100°C. or higher, for 1 minute to 6 hours, preferably it is heated at 100°C. for about 1 to 30 minutes. An effective amount of the composition is withdrawn by aseptic technique using a syringe for administration to a mammal.

(*Id.* at col. 6, ll. 56-67.)

6. Among other attributes of its solubilization aid, Crane discloses:

> The use of PEG, a solubilization aid, facilitates the removal of the ^{99m}Tc-ligand complex from the glassware used in the preparation of the complex and in its purification. It was determined that a solution of 5% PEG in saline is sufficient to remove 91% of the activity off the glassware. This amount was adequate to deliver the amount of activity needed for oncomouse imaging experiments. A solution of 5% PEG in saline has a low enough viscosity to allow for easy injection into the OncoMice™. In parallel experiments, no toxic effects from the PEG solutions were observed in mice, using concentrations below 25% (v/v).

(*Id.* at col. 10, ll. 25-35.)

7. Crane states:

> As used herein ^{99m}Tc-TBI is intended to represent the complex, $^{99m}Tc(TBI)_6^+$, formed by reduction of a ^{99m}Tc species in the presence of TBI. ^{99m}Tc-TBI is considered to be associated with anions present in the composition to achieve a charge neutral salt. One of ordinary skill in the art would recognize the anion(s) present depends upon the pharmaceutical carrier, the reductant used, and the presence of optional components selected from buffers, stabilization aids and lyophilization aids. If saline, for example, was used as the pharmaceutical carrier, then chloride (Cl^-) would be the counterion. Other anions include, but are not limited to, sulphate, acetate, phosphate, citrate, succinate and tartrate.

(*Id.* at col. 4, ll. 16-27.)

8. Yamaguchi discloses "a container for radiopharmaceuticals characterised in that the interior surface of a glass container is coated with silica" (Yamaguchi [0011]).

9. Yamaguchi discloses:

> [T]he silica film coated on the interior surface of the glass container plays a role in preventing the pharmaceutical solution from coming into contact with water-soluble components such as alkalis included in the glass. That is to say, alkali components such as sodium ions (Na^+) and potassium ions (K^+) are present in the glass, and these components might be dissolved by the pharmaceutical solution. It is believed that in this solution state there is an equilibrium between the potassium ions and the glass; a constant amount of potassium ions is always present in solution, but potassium ions themselves change their state back and forth between the free state and the state in which they are bonded to the glass.

(*Id.* at [0013].)

10. Yamaguchi explains:

> When using an aqueous solution containing radioactive thallium chloride (^{201}Tl) as the radiopharmaceutical, since the thallium is present as a monovalent cation and not as a trivalent cation, it can be expected to show the same properties as those of potassium, which is a monovalent cation. Since the thallium ions show the same properties as those of potassium ions, the potassium ions and thallium ions react with the glass competitively. As a result, a constant amount of thallium is always adsorbed on the glass. Therefore, even if a precise amount of the radiopharmaceutical is administered to a patient, it is short by an amount corresponding to the amount of adsorbed thallium and the required amount of the radiopharmaceutical cannot be administered to the patient correctly.

(*Id.* at [0014].)

11. Yamaguchi discloses that "[w]hen the interior surface of the glass container is coated with silica, the dissolution of potassium from the glass can be suppressed, and thus the equilibrium reaction between thallium and potassium is not caused so preventing thallium from being adsorbed thereon" (*id.* at [0015]).

12. Walther discloses that "[l]ow melting glass materials, such as borosilicate glasses or calcium, sodium glasses, corrode in a known manner on contact with water or other liquids. Particularly water withdraws sodium ions from glass" (Walther, col. 1, ll. 19-22).

13. In view of the problem of ions leaching from glass, Walther discloses that "[h]ollow glass bodies, which require an increased chemical resistance for the interior surface, are, for example, those used . . . for components used for biotechnology reactors, and as containers for medicinal purposes (e.g. ampoules, bottles, injector devices, cylindrical ampoules, etc.). The latter mentioned applications are of special significance" (*id.* at col. 1, ll. 27-43).

14. To address the problem of ions leaching from glass Walther discloses "a glass tube made from low melting glass material and acting as a semifinished product for forming a hollow glass body with an interior coating having a high chemical resistance or inertness" (*id.* at col. 1, ll. 13-16).

15. Walther discloses that, for coating the inner surfaces of its tubes, "the following oxides may be used, among others . . . : SiO_2, Al_2O_3, TiO_2 or mixtures thereof" (*id.* at col. 4, ll. 40-42).

16. Walther discloses:

> Because of the invention it is also possible to prepare glass tubes with increased interior chemical resistance so that the predominant part of the surface of the entire system is provided with a high chemical resistance after a possible shaping process, while a comparatively smaller area portion is left with a lesser chemical resistance. Exemplary applications include: glass tubes which are used in biotechnology and are used with media which is absorbed in standard glass surfaces, containers for medical purposes in which the total ion leach out from the container plays an important role, (e.g. for dispensing alkali and other metal ions).

(*Id.* at col. 3, l. 59, through col. 4, l. 2.)

17. Schott Glaswerke discloses that it is "known that with all glass containers, even glass containers that are made of borosilicate glass and which, according to the pharmacopeias (for example, Deutsches Arzneibuch DAB 10 [German Pharmacopoeia]) are classified in the high durability

class, reactions of the glass surface with the solutions can be demonstrated" (Schott Glaswerke 1).[4]

18. Schott discloses that the reaction between glass containers and the solutions inside them "is due primarily to the alkaline substances leaching from the glass surface and caused by the aqueous solution. This leaching during storage may result in an undesired increase in the pH[;] for example, if water for injection purposes is involved, it may [be] several pH units higher" (*id.* at 1-2).

19. To address the problem of ions leaching from glass, Schott discloses "a glass container for storing pharmaceutical or diagnostic solutions that remains largely inert with respect to these solutions, i.e., in which the quantities of ions that leach out of the glass as a result of these solutions is minimized" (*id.* at 2).

20. Schott discloses that the "glass container is coated on the inside, i.e., on the surface that is contact with the solutions, with a layer of oxides and/or nitrides of elements Si, Ti, Ta, Al or mixtures thereof, with the layer being produced by means of the plasma CVD method (PCVD method)" (*id.*).

21. Schott discloses that "[s]urprisingly, it was found that a glass container having coatings in accordance with the PCVD or PICVD method is significantly more resistant to leaching and, as a result, its behavior relative the solutions stored in it is significantly more inert" (*id.*).

[4] This document is not paginated. We therefore refer to the first page as page 1, and the remaining pages as if the document were paginated consecutively.

22. Schott further discloses that "[e]specially suitable are oxidic layers, more particularly layers made of SiO_2 and TiO_2, with SiO_2 being preferred" (*id.* at 3).

PRINCIPLES OF LAW

As the Supreme Court pointed out in *KSR Int' l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Rather, the Court stated:

> [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does* . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

Id. at 418-419 (emphasis added); *see also id.* at 418 (requiring a determination of "whether there was an apparent reason to combine the known elements *in the fashion claimed* by the patent at issue") (emphasis added).

While it recognized the importance of providing a rationale for practicing the claimed subject matter, the Court also reaffirmed that "when a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *Id.* at 417 (quoting *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976)). The Court reasoned that:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable

> solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

Id. at 421.

The Court also noted that the analysis under 35 U.S.C. § 103 properly "take[s] account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418; *see also id.* at 421 ("A person of ordinary skill is . . . a person of ordinary creativity, not an automaton.").

The Court further noted that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it." *Id.* at 421 (citations omitted.)

It is well settled that evidence of unexpected results may rebut an examiner's prima facie case of obviousness. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998); *see also KSR*, 550 U.S. at 416 ("The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams's design was not obvious to those skilled in the art") (discussing *United States v. Adams*, 383 U.S. 39 (1966)).

However, "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

ANALYSIS

Appellants' arguments do not persuade us that the Examiner's conclusion of obviousness is erroneous.

Claim 1 recites a composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface, "the improvement being that the radiopharmaceutical comprises a coordination complex of a metal with an organic ligand." Crane discloses a solution containing the radiopharmaceutical metal-ligand complex ^{99m}Tc-TBI in a vial (FF 5). The solution is for administration to a patient to allow imaging of breast cancer tumors (FF 1).

Thus, Crane differs from claim 1 only in that Crane does not disclose that the vial has a silica coating on its inner surface. However, each of Yamaguchi (preventing adherence of radiopharmaceuticals to containers' inner surfaces (FF 8-11)), Walther (preventing ions from leaching from glass containers into medically administered solutions (FF 12-16)), and Schott (ion leaching/pH change prevention in medical solutions (FF 17-21)), discloses that it is advantageous to provide a silica coating to the inner surfaces of containers that hold medical solutions. We therefore agree with the Examiner that an ordinary artisan following the teachings of Crane, advised by the other references of the advantages of a silica inner coating on containers having the same purpose as Crane's, would have been prompted to place a silica inner coating on Crane's containers.

We acknowledge that, other than containing the radiopharmaceutical solutions, Crane discloses little about the properties of its vials. However, that fact does not render claim 1 any less obvious, given the advantages of silica inner coatings disclosed by the other references. It is well settled that

it is legal error to evaluate a claim's obviousness by using blinders to focus on a single reference while ignoring relevant teachings in other references. *See In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole.").

We acknowledge Yamaguchi's disclosure that its inner coating prevents adsorption of ionic, rather than complexed, radiopharmaceuticals (*see* FF 9-11). We also acknowledge Crane's disclosure of the importance of a solubilization aid in its radiopharmaceutical formulations (*see* FF 2, 3, 6). However, given Walther's and Schott's disclosures of the desirability of rendering inert the inner surfaces of containers of medically administered solutions (FF 13, 16, 18, 19), we cannot agree that an ordinary artisan lacked the impetus to give Crane's vials a silica inner coating.

Moreover, while Appellants aver that the claimed coating provides unexpected results, Appellants point to no comparison between the closest prior art and an embodiment encompassed by the claims. It is well settled that argument by counsel is no substitute for actual evidence. *In re Cole*, 326 F.2d 769, 773 (CCPA 1964); *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997).

In sum, we are not persuaded that the Examiner erred in concluding that an ordinary artisan would have considered it obvious to provide the inner surfaces of Crane's radiopharmaceutical metal complex-containing vials with a silica coating as taught in Yamaguchi, Walther, and Schott Glaswerke. We therefore affirm the Examiner's rejection of claim 1 as

being obvious over those references. Claims 2-5 were not argued separately and therefore fall with claim 1. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Claim 6 recites "[a] kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica coating on the inner surface." As noted above, Crane discloses a kit comprised of a vial that contains the non-radioactive organic ligand tertiary butyl isonitrile, which can be lyophilized or in solution (FF 4).

Thus, Crane differs from claim 6 only in the lack of a silica coating on the container's inner surface. For the reasons discussed above, we agree with the Examiner that an ordinary artisan would have considered such a coating obvious. We therefore also affirm the Examiner's obviousness rejection of claim 6, and its dependent claims 7-9, which were not argued separately.

Claim 10 recites "[a] composition for the preparation of a stabilized radiopharmaceutical metal complex which comprises (i) a stabilizer capable of stabilizing said radiopharmaceutical metal complex; and (ii) an organic ligand which forms a coordination complex with the metal; in a container which has a silica coating on the inner surface." As noted above, in addition to solubilization aids, buffers, and bacteriostats, any of which can be considered stabilizers, Crane's metal complex-containing solutions may also include "stabilization aids" (*see* FF 3).

Thus, Crane differs from claim 10 only in the lack of a silica coating on the container's inner surface. As discussed above, we agree with the Examiner that an ordinary artisan would have considered such a coating

obvious. We therefore also affirm the Examiner's obviousness rejection of claim 10, and its dependent claims, which were not argued separately.

Claim 11 recites "[a] composition for the preparation of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface." As noted above, Crane includes a bacteriostat in its compositions (FF 3), and therefore differs from claim 11 only in the lack of a silica coating on the container's inner surface.

As discussed above, we agree that an ordinary artisan would have considered such a coating obvious, and therefore affirm the Examiner's obviousness rejection of claim 11, and its dependent claims, which were not argued separately.

In sum, we affirm the Examiner's rejection of claims 1-14 under 35 U.S.C. § 103(a) as being unpatentable over Crane and Yamaguchi in view of Schott Glaswerke or Walther.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc

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